

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/036965

A. CLASSIFICATION OF SUBJECT MATTER  
INV. A61K9/14 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 800 666 A (ELAN PHARMA INT LTD [IE]) 27 June 2007 (2007-06-27) the whole document	1-86
X	WO 03/080027 A (ELAN PHARMA INT LTD [US]; MERISKO-LIVERSIDGE ELAINE [US]; BOSCH H WILL) 2 October 2003 (2003-10-02) the whole document	1-86
X	WO 02/24163 A (ELAN PHARMA INTERNAT LTD ; RUDDY STEPHEN B (US); RYDE NIELS P (US)) 28 March 2002 (2002-03-28)	1,2,4-86
Y	page 9, line 18 - line 20 example 4; tables 5,6	1-86
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☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

19 June 2009

Date of mailing of the international search report

29/06/2009

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# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2009/036965

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 499 299 A (STERLING WINTHROP INC) 19 August 1992 (1992-08-19) cited in the application page 3, line 19 - line 38	1,2,4-86
Y	page 3, line 54 - page 4, line 9 page 4, line 16 - page 5, line 32 page 13, line 48 - line 50 examples See p.4, 1.5: tamoxifen, medroxyprogesterone	1-86
X	EP 0 577 215 A (STERLING WINTHROP INC) 5 January 1994 (1994-01-05) cited in the application page 2, line 45 - page 3, line 26	1,2,4-86
Y	page 3, line 49 - page 4, line 9 page 4, line 37 - line 58 examples 11-16 See p.3, 1.9 ff: taxol, medroxyprogesterone, ethynylestradiol, tamoxifen, thalidomide	1-86
Y	US 2002/002294 A1 (CUSHMAN MARK ET AL) 3 January 2002 (2002-01-03) page 1, paragraphs 5,7 page 3, paragraphs 29,37 page 4, paragraphs 45,46; examples 4,5; tables 1,2 See tables 1 and 2: 2-methoxyestradiol, 17-ethynylestradiol	1-86
Y	US 6 068 858 A (LIVERSIDGE GARY G ET AL) 30 May 2000 (2000-05-30) cited in the application column 7, line 25 - line 32 column 7, line 66 - column 8, line 28 examples 8,9	1-86
Y	US 5 510 118 A (SWANSON JON R ET AL) 23 April 1996 (1996-04-23) cited in the application column 5, line 39 - line 41 claim 1; table I	1-86
Y	WO 90/15593 A (YTKEMISKA INST) 27 December 1990 (1990-12-27) page 3, line 18 - line 34 page 5, line 22 page 7, line 29 examples	1-86

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## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-86 in part

Present independent claims 1, 34 and 54 relate to an extremely large number of possible compositions (combination of nanoparticles of an "angiogenesis inhibitor" and a "surface stabilizer", any combination being possible with no particular limitation). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compositions claimed, namely those wherein the angiogenesis inhibitor is 2-methoxyestradiol, for the following reasons:

The technical problem to be solved is the provision of stable nanoparticulate dispersions of angiogenesis inhibitors comprising a surface stabilizer wherein the nanoparticles (having a mean particle size of less than 2000 nm) do not aggregate/agglomerate significantly following storage, i.e. the mean particle size of the nanoparticulate dispersions does not significantly grow upon storage. The problem of particle aggregation in nanoparticulate dispersions depends on surface interactions between the particles. It is obvious that such surface interactions will be different for different active agents and different surface stabilizers as a function of their physicochemical characteristics. Not all surface stabilizers will function to produce a non-agglomerated nanoparticulate composition for all active agents. The application provides data showing that the relevant technical problem is solved for 2-methoxyestradiol by means of stable nanocrystalline dispersions of said compound and a surface stabilizer such as HPC, HPMC, lysozyme, or copovidonum possibly in combination with docusate sodium (DOSS) (see the examples). However, claim 2 recites a large list of other possible angiogenesis inhibitors, and claims 12-14 recite a large list of other possible surface stabilizers, having very different physicochemical properties. The content of the application does not provide any evidence at all in order to make credible that the relevant technical problem is also solved for each one of the possible angiogenesis inhibitor-surface stabilizer combinations claimed. Therefore, nanoparticulate dispersions of the angiogenesis inhibitors recited in claim 2 other than 2-methoxyestradiol are not considered to be sufficiently disclosed in the application.

Accordingly, in the present case claims 1, 34 and 54 so lack support, and/or the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and sufficiently disclosed, namely those parts relating to the compositions wherein the angiogenesis inhibitor is 2-methoxyestradiol in the sense of claim 3, and wherein the surface stabilizer comprises a polymer as above (see examples).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO

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**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

## INTERNATIONAL SEARCH REPORT

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PCT/US2009/036965**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: **1-86 in part**  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

**1. claims: 1-86 in part**

**A nanoparticulate composition comprising an angiogenesis inhibitor (particle size less than 2000 nm), and a surface stabilizer. Each single active agent defined in claim 2**

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
  
2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

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## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-86 in part

A nanoparticulate composition comprising an angiogenesis inhibitor (particle size less than 2000 nm), and a surface stabilizer. Each single active agent defined in claim 2 represents a separate invention.

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1800666	A	27-06-2007	NONE	
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## INTERNATIONAL SEARCH REPORT

Information on patent family members

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